


Biological Roles and Mechanisms of Circular RNA in Human Cancers

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Abstract: Circular RNA (circRNA) is an intriguing class of RNA with covalently closed-loop structure and is highly stable and conservative. As new members of the ncRNAs, the function, mechanism, potential diagnostic biomarker, and therapeutic target have raised increased attention. Most circRNAs are presented with characteristics of abundance, stability, conservatism, and often exhibiting tissue/developmental-stage-specific manner. Over 30,000 circRNAs have been identified with their unique structures to maintain stability more easily than linear RNAs. An increased numbers of circRNAs are dysregulated and involved in several biological processes of malignance, such as tumorigenesis, growth, invasion, metastasis, apoptosis, and vascularization. Emerging evidence suggests that circRNAs play important roles by acting as miRNA sponge or protein scaffolding, autophagy regulators, and interacting with RNA-binding protein (RBP), which may potentially serve as a novel promising biomarker for prevention, diagnosis and therapeutic target for treatment of human cancer with great significance either in scientific research or clinic arena. This review introduces concept, major features of circRNAs, and mainly describes the major biological functions and clinical relevance of circRNAs, as well as expressions and regulatory mechanisms in various types of human cancer, including pathogenesis, mode of action, potential target, signaling regulatory pathways, drug resistance, and therapeutic biomarkers. All of which provide evidence for the potential utilities of circRNAs in the diagnosis and treatment of cancer.

Keywords: circRNA, cancer, miRNA sponge, protein scaffolding, gene splicing and transcription, biomarker, therapeutic target

Introduction

CircRNA has a covalent closed-loop structure and is highly stable and conservative special RNA, which exists widely in various tissues and organs with variable expression levels, and broadly participates in the occurrence and development of diseases including cancer in various ways. Currently, with the development of deep RNA sequencing (RNA-seq) technologies and novel bioinformatic approaches, over 30,000 circRNAs have been identified with the unique structures and have attracted increasing attention given its high biological and functional interest. CircRNAs are resistant to exonuclease RNase R and maintain stability more easily than linear RNAs. Increasing evidences have shown that part of circRNAs containing miRNA binding sites may act as sponge to interact with miRNA and regulate its biological functions, thereby affecting the expression and function of its downstream target genes.^{1,2} CircRNAs with binding sites of enzymes and substrates may act as proteins scaffolding to mediate the interaction of protein-protein. For

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example, circFoxo3, containing the binding sites of mouse double minute 2 (MDM2) and p53, was involved in the interaction between MDM2 and p53 by functioning as a protein scaffold.^{3,4} Moreover, circRNA also play important roles in regulating biological functions of cancers through involvement in gene alternative splicing, transcription and translation, cell autophagy and interacting with RNA-binding proteins (RBPs).⁴⁻⁶ In this review, we describe the major biological functions and clinical relevance of circRNAs, as well as its expression and regulatory mechanisms in various types of human cancer including pathogenesis, mode of action, potential target, signaling regulatory pathways, therapeutic biomarkers, drug resistance and clinical application.

Major Features of circRNAs

CircRNAs, first identified in RNA viruses in 1976⁷ and once considered “splicing noise” in organisms, have recently become interest research focus as the results of improvements in high-throughput sequencing technology and bioinformatics, circRNAs have become a research hotspot.⁴ As a new type of RNA molecule, circRNAs are single-stranded circularized RNA with no 5' caps and 3' poly(A) tails; and commonly generated from the precursor mRNA (pre-mRNA) by a process called back-splicing in which an upstream acceptor site is joined with a donor site.⁸ Most circRNAs are evolutionarily conserved across species.⁹ The vast majorities of circRNAs are often located in the cytoplasm, which are derived from known protein-coding genes containing one or several exons that are toward the 5' of the gene and are flanked by longer introns. The long introns containing flank regions that will become circRNAs usually contain specific sequences which induce circRNA formation either by complementarity and/or by binding to circRNA-promoting factors, and are generally expressed in cell type-specific and tissue-specific manners.^{10,11} Based on the different structures, and cycling mechanisms, circRNA molecules are divided into four categories: exonic circRNAs (ecRNAs), intronic circRNAs (ciRNAs), exon-intron circRNAs (elciRNAs), and intergenic circRNAs. Unlike linear RNAs, circRNAs are stable and resistant to exonucleases (including RNase R) due to the lack of a poly(A) tail and have longer median half-life than that of their linear mRNAs due to the lack of free 3' or 5' ends, which makes them resistant to regular mechanisms of linear RNA decay.¹⁰⁻¹²

Functions of circRNAs

Acting as miRNA Sponges

Accumulating evidence has revealed that numerous circRNAs regulate gene expression by functioning as miRNA sponge molecules. Compared with other competing endogenous RNAs (ceRNAs) (such as lncRNA or pseudogenes), circRNAs exhibit a greater preference to bind to miRNAs and are called “super sponges.”¹³ Many circRNAs contain miRNA response elements and binding sites, therefore, acting as “miRNA sponge” is the most important function and mechanism of regulating the growth and progression of human cancer (Figure 1). For example, circ_0004771 was identified to restrain cell proliferation and accelerate cell apoptosis in breast cancer cells. circ_0004771 acted as a miRNA sponge to decrease expression of miR-653, this in turn targeted mesenchymal marker zinc finger E-box-binding homeobox 2 (ZEB2) gene expression by binding to its 3'-untranslated region (3'UTR) of ZEB2 mRNA.¹⁴ In addition, circAGFG1 was correlated with advanced clinical stage, poor prognosis and pathological grade of triple-negative breast cancer patients, mechanistically, circAGFG1 might directly sponge miR-195-5p, which targeted and repressed cyclin E1 expression.¹⁵

Regulating Gene Splicing, Transcription and Translation

Although most circRNA is located in cytoplasm, some are still existed in nucleus. The part of circRNA retained in nucleus acted as transcriptional or splicing regulators to interfere with gene expression and involved in alternative splicing and transcription process (Figure 2). For example, circPOK, derived from the Zbtb7a gene in tumor cells, was involved in gene transcription by encoding the pokemon transcription factor, thereby regulating the proliferative and pro-angiogenic factors through activating the interleukin enhancer-binding factor 2 and 3 complex (ILF2/3) complex.¹⁶ Moreover, circITGA7 was found to increase the transcription of its host gene integrin alpha 7 (ITGA7) by inhibiting a transcription factor RAS-responsive element-binding protein 1 (RREB1) through Ras pathway.¹⁷ In addition, circ-UBR5 was significantly decreased in non-small cell lung cancer (NSCLC) tissues and associated with tumor differentiation. Mechanically, circ-UBR5 might be involved in RNA splicing regulatory process through binding to splicing regulatory factor QKI, NOVA alternative splicing regulator 1 (NOVA1) and U1

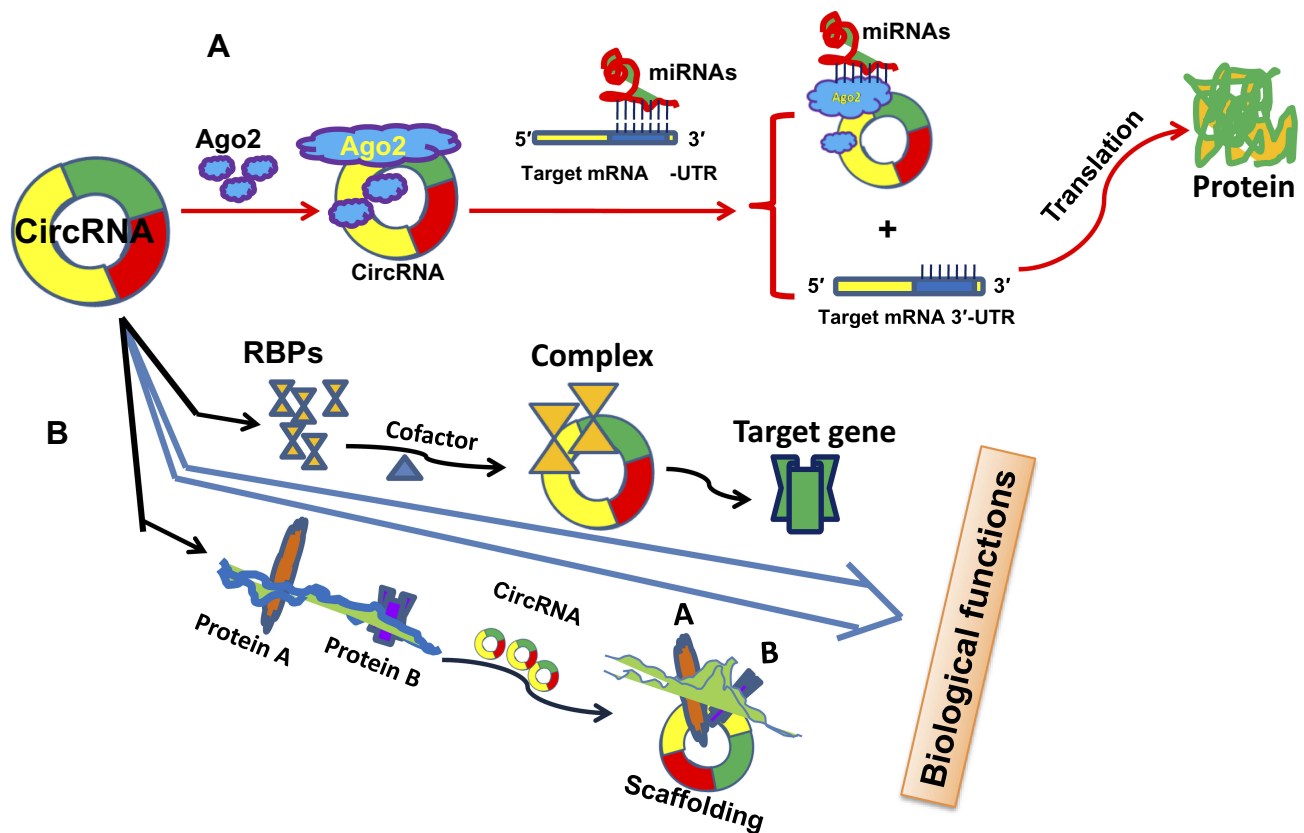


Figure 1 circRNAs involve in cancer progression by acting as “miRNA sponge” or protein scaffolding. (A) circRNAs competitively bind to miRNA with the participation of Ago2 protein by acting as “miRNA sponge,” consequently release the target gene of miRNA. (B) circRNAs directly interact with RNA-binding proteins (RBPs), or mediate the interaction between proteins by serving as protein scaffolding to regulate the expression of downstream targets.

small nuclear RNA (snRNA) in the NSCLC cells.¹⁸ Furthermore, circRNA containing AUG sites and open reading frame (ORF) could be driven by the internal ribosome entry site (IRES) and translated into the functional protein (Figure 2). However, the relevance of role of circRNA translational function needs to be further explored in terms of mediating occurrence and progression of human cancer.^{3,4} Overall, gene alternative splicing, transcription and translation are important processes to exert biological functions in cancers, while circRNA plays a crucial role in these processes (Figure 2).

Acting as Autophagy Regulator

Autophagy is a highly conserved and successive self-degradative process that plays an important role in cellular stress responses and survival, which often occurs during tumorigenesis, progression, metastasis and chemotherapy leading to drug resistance in the treatment of cancer.^{19,20} Emerging evidence showed that circRNA was involved in the tumor autophagy affecting occurrence and progression of human cancer (Figure 2). For example, circHIPK3 was found

to act as an autophagy regulator in STK11 mutant lung cancer cells. The results showed that missing expression of circHIPK3 could induce cell autophagy through regulating the miR124-3p/signal transducer and activator of transcription 3 (STAT3)/protein kinase AMP-activated catalytic subunit alpha 2 (PRKAA)/AMP-activated protein kinase (AMPK α) signaling regulatory pathways. Moreover, the ratio of circHIPK3 to linHIPK3 (linear HIPK3) reflected the level of autophagy in cancer cells.²¹ Moreover, circ_104075 was correlated with apoptosis and autophagy of glioma cells. Overexpression of circ_104075 neutralized the inhibitory effects of matrine on proliferation and promoted the cell autophagy in glioma U251 cells.²² Nevertheless, the research of circRNA in the tumor autophagy process is still in the initial stage, the true role and function, potential mechanism underlying this required to be explored in the future.

Interacting with RNA-Binding Proteins (RBPs) and Acting as Protein Scaffolding

RNA-binding proteins (RBPs) are a group of proteins widely involved in gene transcription and translation.

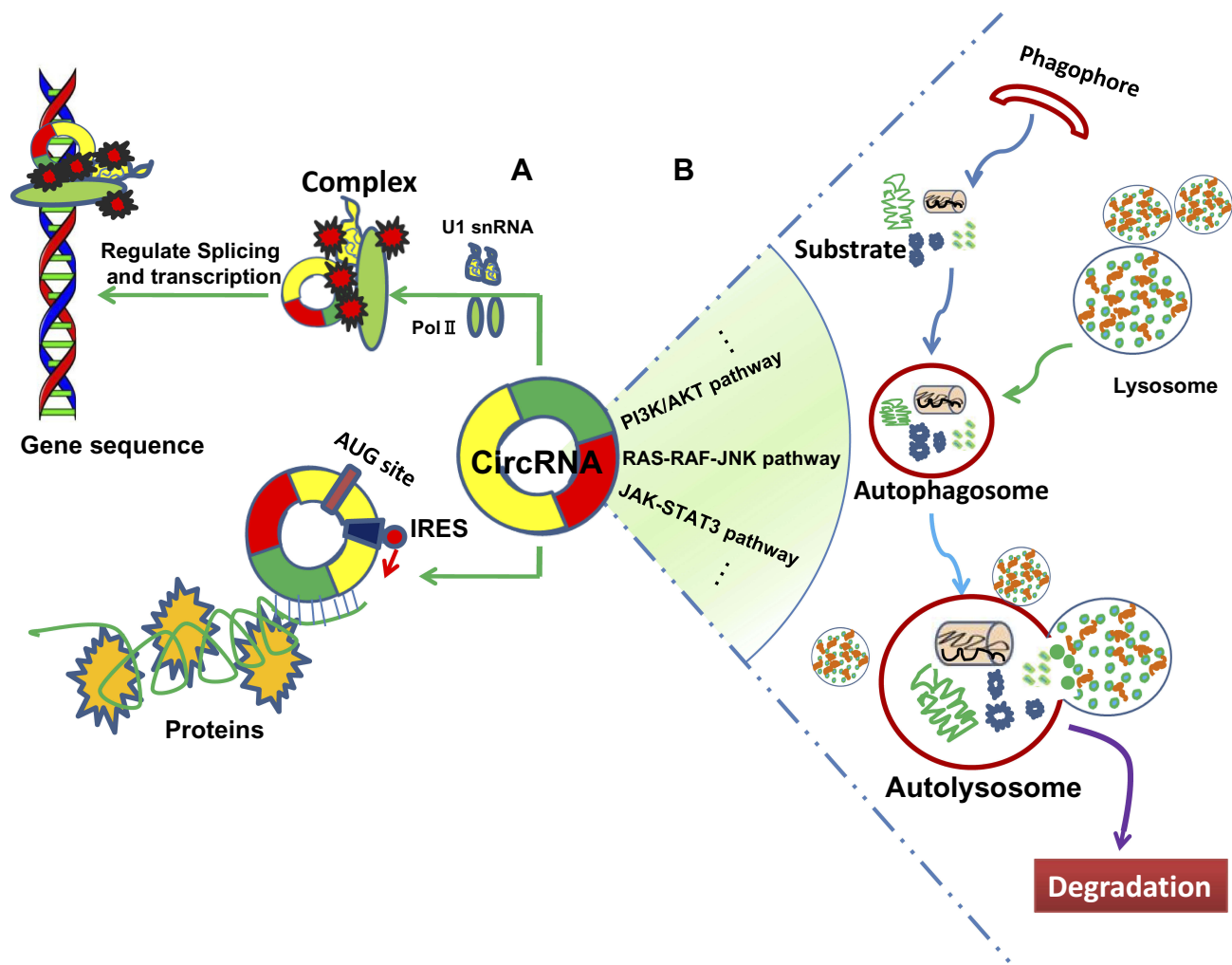


Figure 2 circRNAs involve in cancer progression by regulation of gene splicing, transcription, translation and cell autophagy. **(A)** circRNAs influence the progression of human cancers by regulating gene splicing, transcription and translation via interaction with U1 small nuclear RNA (snRNA), RNA polymerase II (Pol II), and alternative splicing regulator. Moreover, circRNA containing AUG sites and open reading frame (ORF) driven by the internal ribosome entry site (IRES) may translate into the functional protein. **(B)** circRNAs are associated with the tumor cell autophagy through regulating the autophagy-related signaling pathways.

Increasing evidences suggested that circRNA could bind RBPs and affect its function²³ (Figure 1). CircRNA could also sequester, store and sort RBPs and thus control the intracellular localization.^{24,25} Conversely, RBPs could also regulate the function and expression level of circRNA. RNA-binding protein 3 (RBM3) dynamically regulated the production of SCD-circRNA2, rooted in the 3'-UTR of the stearoyl-CoA desaturase (SCD) gene, thereby ultimately regulating proliferation in hepatocellular carcinoma cells.²⁶ Recent studies have shown that RBP quaking could also modulate the formation of circRNA through forming RNA-protein complexes (RPCs).²⁷ Moreover, RNA-binding motif protein 20 (RBM20) was associated with the formation of subset of circRNAs and formed the class of RBM20-dependent circRNAs.²⁸ Thus, circRNA and RBPs are closely associated with each other in the

occurrence and development of cancer. Overall, circRNAs are abnormally expressed and related to the occurrence and progression of human cancer via influencing cell growth, proliferation, migration, invasion, and other pathological processes (Table 1). In addition, circRNAs were also correlated with clinical relevance, such as TNM stage, lymph node metastasis, differentiation, tumor size and overall survival (Table 2). All of these provided evidences for the potential biomarker and therapeutic target in the diagnosis and treatment of human cancers. In addition to interacting with RBPs, another function of circRNA is its interaction with protein. It can function as protein sponges by adsorbing one or more proteins via the binding sites, thereby directly mediating the interaction between proteins by acting as protein scaffolding, thus regulating gene expression (Figure 1). For example, cyclin-dependent

Table 1 Expression and Functional Characterization of circRNAs in Cancers

Type of Cancers	Name of circRNAs	Levels	Target Genes	Mode of Functions	Functional Phenotypes	References
Lung cancer	Circ-UBR5	Down	QK/NOVA1/ UI snRNA	Regulate RNA splicing	Correlate with tumor differentiation	[18]
	CircNOL10	Down	SCML1	Regulate transcription	Inhibit cell proliferation and promote cell apoptosis	[38]
	CircPTPRA	Down	miR-96-5p	MiRNA sponge	Suppress EMT and invasion	[39]
	Circ_0012673	Up	miR-22	MiRNA sponge	Promote cell proliferation	[53]
	Circ_0007766	Up	Cyclin	Cell cycle regulator	Induce the cell proliferation and migration	[59]
Breast cancer	CircRNA-MTO1	Down	TRAF4/Eg5	Regulate gene translation	Suppress cell viability and reverse monastrol resistance	[67]
	CircTADA2A-E6	Down	miR-203a-3p	MiRNA sponge	Suppress breast cancer progression and metastasis	[68]
	CircPLK1	Up	miR-296-5p	MiRNA sponge	Promote cell growth and invasion	[70]
	CircBMPR2	Down	miR-553	MiRNA sponge	Inhibit cell proliferation migration and invasion	[72]
Colorectal cancer	CircITGA7	Down	ITGA7	Regulate gene transcription	Inhibit cell growth and metastasis	[17]
	Circ_0009361	Down	miR-582	MiRNA sponge	Suppress colorectal cancer progression	[81]
	Circ_001569	Up	miR-145	MiRNA sponge	Promote cell proliferation and invasion	[88]
Esophageal Squamous Cell Carcinoma	Circ-PRKCI	Up	miR-3680-3p	MiRNA sponge	Stimulate cell migration and proliferation	[95]
	CiRS-7	Up	miR-7	MiRNA sponge	Promote growth and metastasis	[98]
	Circ_0000337	Up	miR-670-5p	MiRNA sponge	Promote cell proliferation, migration and invasion	[99]
Gastric cancer	CircYAPI	Down	miR-367-5p	MiRNA sponge	Suppress cell proliferation and invasion	[105]
	Circ-NOTCH1	Up	miR-637	MiRNA sponge	Enhance cell proliferation and invasion; reduce apoptosis;	[108]
	Circ-DONSON	Up	NURF complex	Protein scaffolding	Facilitate gastric cancer growth and invasion	[119]
	CircAGO2	Up	HuR protein	Interact with RBPs	Promote the tumorigenesis and aggressiveness	[120]
Hepatocellular carcinoma	Circ_0101432	Up	miR-1258/miR- 622	MiRNA sponge	Inhibit cell apoptosis, promote cell proliferation and invasive	[126]
	CircZNF652	Up	miR-203/miR- 502-5p	MiRNA sponge	Promote cell metastasis	[127]
	Circ_101280	Up	miR-375	MiRNA sponge	Promote cell proliferation and suppress apoptosis	[134]
	CircSLC3A2	Up	miR-490-3p	MiRNA sponge	Promote cell proliferation and invasion;	[135]

(Continued)

Table 1 (Continued).

Type of Cancers	Name of circRNAs	Levels	Target Genes	Mode of Functions	Functional Phenotypes	References
	CircARSP91	Down	ULBPI	Immune-association	Increase cell susceptibility to NK cell cytotoxicity;	[137]
Bladder cancer	CircBCRC-3	Down	miR-182-5p	MiRNA sponge	Suppress cell proliferation	[150]
	CircUVRAG	Up	miR-223	MiRNA sponge	Inhibit cell growth and metastasis	[151]
	CircGprc5a	Up	Gprc5a-Peptide	Peptide-dependent manner	Promote Bladder Oncogenesis and Metastasis	[156]
Pancreatic cancer	Circ_0006215	Up	miR-378a-3p	MiRNA sponge	Promote cell viability, apoptosis and migration	[161]
	CircRNA_100782	Up	miR-124	MiRNA sponge	Promote cell proliferation	[162]
	CircZMYM2	Up	miR-335-5p	MiRNA sponge	Promote cell proliferation and induce cell apoptosis	[163]
	CircRHOT1	Up	miR-26b/miR-125a/miR-330	MiRNA sponge	Promote cell proliferation and cell invasion	[164]
Papillary thyroid carcinoma	CircBACH2	Up	miR-139-5p	MiRNA sponge	Promote cell proliferation, migration and invasion	[172]
	CircRAPGEF5	Up	miR-198	MiRNA sponge	Promote cell proliferation, migration and invasion	[173]
	CircRNA_102171	Up	CTNBNBPI	Protein scaffolding	Promote cell proliferation, migration and invasion; promote cell apoptosis.	[175]
	Circ-ITCH	Down	miR-22-3p	MiRNA sponge	Suppress cell proliferation and invasion; Promote cell apoptosis	[176]
Osteosarcoma	CircFAT1	Up	miR-375	MiRNA sponge	Promote cell migration, invasion and tumorigenesis	[186]
	CircTADA2A	Up	miR-203a-3p	MiRNA sponge	Promotes tumor progression and metastasis	[188]
Glioblastoma	Circ_0001946	Down	miR-671-5p	MiRNA sponge	Reduce cell proliferation, migration	[191]
	CircNT5E	Up	miR-422a	MiRNA sponge	Promote cell proliferation, migration and invasion	[193]
	Circ-SHPRH	Down	SHPRH-146aa	Protein translation	Suppress tumor progression and tumorigenesis	[196]
Ovarian cancer	circPUM1	Up	miR-615-5p and miR-6753-5p	MiRNA sponge	Promote cell proliferation, migration and invasion and inhibited cell apoptosis	[199]
	circWHSC1	Up	miR-145 and miR-1182	MiRNA sponge	Promote cell proliferation, migration and invasion and inhibited cell apoptosis	[200]
	circ_0061140	Up	miR-370	MiRNA sponge	Promote cell proliferation, migration and the EMT	[207]
Prostate cancer	circUCK2	Down	miR-767-5p	MiRNA sponge	Inhibit cell invasion and proliferation	[217]
	circFOXO3	Up	miR-29a-3p	MiRNA sponge	Promote cell cycle, proliferation and inhibit cell apoptosis	[218]

(Continued)

Table 1 (Continued).

Type of Cancers	Name of circRNAs	Levels	Target Genes	Mode of Functions	Functional Phenotypes	References
	circHIPK3	Up	miRNA-338-3p	MiRNA sponge	Inhibit the proliferative and invasive	[220]
Myeloid leukemia	circ_0009910	Up	miR-20a-5p	MiRNA sponge	Promote cell proliferation and induced apoptosis	[229]
	circ_100290	Up	MiR-203	MiRNA sponge	Promote cell proliferation and inhibit apoptosis	[230]

Note: The expression, molecular targets, functional phenotypes of circRNA in different cancers were summarized.

kinase 2 (CDK2) and p21 proteins were associated with cell cycle regulation in tumor. CircFOXO3 could mediate the formation of circFOXO3-p21-CDK2 ternary complex by serving as scaffolding, which blocked the function of CDK2, thereby affecting the cell cycle progression of cancer.²⁹

circRNAs in Human Cancers

Lung Cancer

Lung cancer is the leading cause of cancer death and accounts for approximately 13% of all cancer cases and 23% of all cancer-related deaths worldwide.³⁰ Increasing evidence suggested that circRNA might participate in the cell proliferation, migration and invasion of lung cancer, and serve as an important diagnostic marker for the treatment of lung cancer.^{31–37} For example, circNOL10 increased the expression of transcription factor sex comb on midleg-like 1 (SCML1) by inhibiting ubiquitination and regulating the humanin (HN) polypeptide family through affecting multiple signaling pathways. This ultimately inhibited proliferation and induced cell cycle arrest in lung cancer cells.³⁸ Recent study revealed that circPTPRA suppressed the epithelial-mesenchymal transition (EMT) and metastasis of NSCLC cells by sponging miR-96-5p, thereby regulating the expression of downstream tumor suppressor ras association domain family 8 (RASSF8) gene.³⁹ In line with this, other circRNAs, such as circP4HB, circMTO1, circ_0026134, circ-FOXM1, circ_003645, circ_0006427, circABC10, circ-BANP, circFADS2, circ_103809, circMAN2B2, circ_0012673 and circ_0020123 showed similar roles that were served as sponge of miRNAs to regulate the occurrence and development of lung cancer.^{40–54} Emerging evidences demonstrated that cancer-associated chromosomal translocations and encoding fusion gene could generate circRNA, contributing to

tumorigenesis.⁵⁵ For instance, SLC34A2-ROS1 fusion gene could produce circRNA F-circSR, which promoted cell migration of NSCLC cells.⁵⁶ CircRNA F-circEA-2a, and circRNAF-circEA deriving from oncogenic fusion gene echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK), enhanced the cell migration and invasion in NSCLC, and might act as a novel liquid biopsy biomarker in NSCLC.^{57,58} Moreover, some circRNAs regulated cell pathogenesis, development and prognosis of lung cancer by affecting the cell cycle-related signaling pathway. Circ_0007766 induced the proliferation and migration of lung cancer cells through regulating and modulating the cyclin D1/cyclin E1/CDK4 regulatory axis.⁵⁹ Also, others were involved in the influencing the expression of apoptosis-related protein, circVANGL1 contributed to proliferation, migration, invasion, and progression of NSCLC via competing endogenous RNA (ceRNA), becoming a sink for miR-195 thereby modulating the expression of Bcl-2 in NSCLC cells.⁶⁰ Overall, circRNA have been involved in the pathogenesis, development and prognosis of lung cancer, and provided potential biomarker and prospective targets for lung cancer treatment.

Breast Cancer

Breast cancer (BC) is one of the leading causes of cancer-related mortality and the second most common cancer in females. Recently, an increasing number of circRNAs have been identified and correlated with clinical-pathological characteristics in the progression of BC. CircRNAs also participated in the biological functions and progression of BC, such as tumorigenesis, proliferation, apoptosis, cell cycle, vascularization, invasion, migration and metastasis.^{61–65} For example, circ_001569 was identified to be associated with clinical-pathological features and prognosis in BC patients, and knockdown of circ_001569 remarkably

Table 2 The Roles in Clinical Relevance and Prognosis of circRNAs in Human Cancers

Type of Cancers	Name of circRNAs	Levels	Clinical Relevancies	References
Lung cancer	Circ_0016760	Up	Associated with advanced TNM stages, lymph node metastasis and adverse prognosis	[42]
	CircFADS2	Up	Correlated with advanced TNM stage, lymph node metastasis, poor differentiation, tumor size and shorter overall survival	[46]
	Circ-FOXMI	Up	Associated with lymph node invasion, higher TNM stage and unfavorable prognosis.	[48]
	CircMTO1	Down	Associated with malignant features and prognosis	[50]
	Circ_003645	Up	Related to advanced TNM stages, positive lymph node invasion and unfavorable prognosis	[51]
	Circ_0020123	Up	Correlated with positive lymph node metastasis, advanced TNM stages, and adverse prognosis	[54]
	CircVANGL1	Up	Associated with tumor size, TNM stage and overall survival	[60]
Breast cancer	CircANKS1B	Up	Associated with lymph node metastasis and advanced clinical stage	[65]
	CircKIF4A	Up	Associated with tumor size, lymph node metastasis and TNM Stage	[69]
	Circ-UBE2D2	Up	Associated with tumor size, lymph node metastasis and TNM Stage and differentiation	[71]
	Circ_0025202	Down	Correlated with lymphatic metastasis and histological grade	[73]
	Circ_001783	Up	Correlated with tumor size, lymph node status, TNM stage, ER status, PR status, molecular subtype and Ki-67 index	[76]
Colorectal cancer	CircVAPA	Up	Correlated with tumor size, Lymphovascular invasion, Differentiation, Distant metastasis lymph node metastasis and TNM stage	[82]
	Circ_0026344	Down	Correlated with CRC advance and lymphoid node metastasis	[86]
	CircHIPK3	Up	Correlated with Pathological T category, Lymph node metastasis, Distant metastasis and TNM stage	[87]
Esophageal Squamous Cell Carcinoma	Circ-TTC17	Up	Associated with TNM stage and Lymph node metastasis	[94]
	Circ_0006168	Up	Associated with lymph node metastasis and TNM stage	[96]
	Circ-DLGI	Up	Associated with TNM stage	[97]
Gastric cancer	CircNRIP1	Up	Associated with Lymphatic invasion and tumor size	[106]
	Circ_006100	Up	Associated with TNM stage, poor cell differentiation and lymphnode metastasis	[107]
	Circ-DCAF6	Up	Associated with deeper tumor invasion, positive lymph node metastasis and higher TNM stages	[109]
Hepatocellular carcinoma	Circ-ZEB1.33	Up	Associated with HBV infection, TNM stages and tumor size	[124]
	CircDAMTS13	Down	Associated with cirrhosis, tumor size and stage	[132]
	CircTRIM33-12	Down	Associated with tumor size, encapsulation invasion, vascular invasion and tumor number	[136]
Bladder cancer	CircCEP128	Up	Associated with tumor size, TNM stage and Lymphatic metastasis	[149]
	Circ-BPTF	Up	Associated with histological grade and prognosis	[152]
	Circ-cTFRC	Up	Associated with tumor stage, grade, number of tumors and Lymphatic metastasis	[154]
	CircUBXN7	Down	Associated with tumor grade and Pathology stage	[155]
Pancreatic cancer	Circ-PDE8A	Up	Correlated with lymphatic invasion, TNM stage and survival rate	[165]
Papillary thyroid carcinoma	CircZFR	Up	Correlated with TNM stage and overall survival	[177]

(Continued)

Table 2 (Continued).

Type of Cancers	Name of circRNAs	Levels	Clinical Relevancies	References
Osteosarcoma	CircCDR1	Up	Correlated with tumor size, localization, stage and metastasis	[187]
Glioblastoma	Circ_0029426	Up	Correlated with tumor grade	[194]
Ovarian cancer	circSETDB1	Up	Associated with advanced clinical stage, lymph node metastasis and increased chemoresistance	[209]
Prostate cancer	CircITCH circABCC4	Down Up	Related with preoperative PSA, tumor stage and Gleason score Correlated with advanced stage, metastasis and overall survival	[216] [219]
Myeloid leukemia	Circ-Foxo3 circ_100053	Down Up	Correlated with overall survival Associated with clinical stage, BCR/ABL mutant status and imatinib resistance	[233] [236]

Note: The role of circRNA in clinical relevance and prognosis in different cancers was summarized.

inhibited the activation of PI3-K/Akt signal pathway,⁶⁶ Moreover, circRNA-MTO1 (also known as circRNA-007874) could significantly suppress cell viability and reverse monastrol resistance in BC. Mechanistic studies showed that circRNA-MTO1 reduced the Eg5 protein expression but not mRNA level through preventing TNF α receptor-associated factor (TRAF) 4 from activating Eg5 translation.⁶⁷ CircRNAs were also widely involved in the occurrence and development of BC by acting as “miRNA sponge.” For instance, circTADA2A-E6 could sponge miR-203a-3p to reduce the expression of miR-203a-3p; thereby restoring the expression of suppressor of cytokine signaling 3 (SOCS3), a target gene of miR-203a-3p, resulting in suppressed the progression and metastasis of BC.⁶⁸ In addition, circKIF4A promoted proliferation and migration of triple-negative breast cancer (TNBC), cells by directly sponging miR-375 to relieve the suppression of KIF4A target gene.⁶⁹ Moreover, more circRNAs, such as circPLK1, circUBE2D2, circBMPR2, circ_0025202, circ_0103552, circ_0072309, circ_001783, involved in the occurrence and development of BC by acting as miRNA sponge have been reported.^{70–76} Together, circRNA is broadly expressed in BC tissues and cells with variable levels associated with clinical pathogenesis of BC, and could be used as a potential biomarker and therapeutic target in the treatment of BC.

Colorectal Cancer

Colorectal cancer (CRC) is the third most common malignant cancer and the fourth leading cause of cancer death around the world.⁷⁷ In recent years, circRNA is considered as an important regulator for the tumorigenesis and progression in CRC. CircRNA was reported to

be associated with the development of CRC, and acted as potential biomarkers and therapeutic target for the diagnosis and treatment of CRC.⁷⁸ Recently, circRNA expression profiles in CRC patients were performed through high-throughput RNA sequencing (RNA-seq) and total of 448 significantly dysregulated circRNAs were identified. Among those, 394 were up-regulated and 54 were down-regulated, all of which were involved in cell proliferation, migration, invasion and apoptosis in CRC.⁷⁹ circRNA-0000523 activated the activity of Wnt/ β -catenin signaling pathway to regulate the proliferation and apoptosis of CRC cells by sponging miR-31.⁸⁰ Also, circ_0009361 acted as the sponge of miR-582 to enhance the expression of adenomatous polyposis coli 2 (APC2) and blocked the Wnt/ β -catenin signaling; resulting in suppressing cell growth and metastasis of CRC.⁸¹ Furthermore, many other circRNAs, such as circVAPA, circ_0136666, circRNA_103809, circRNA_100290, circ_0026344, circHIPK3, and circ_001569 were also acted as sponge of miRNAs to regulate the tumorigenesis and progression of CRC have been reported.^{82–88} In addition, circRNA was also associated with chemoradiation resistance (CRR) of CRC. One study showed that among 71 circRNAs expressed in 5-FU chemo-resistant CRC cells by microarray analysis, 47 circRNAs were increased and 24 circRNAs were decreased significantly. The study provided a useful database for further understanding of CRR and presented potential targets to reverse CRR in CRC.⁸⁹ To this end, circRNA play an important role in the occurrence and development of CRC, and could also be involved in diagnosis and treatment of CRC.

Esophageal Squamous Cell Carcinoma

Esophageal squamous cell carcinoma (ESCC) is the globally predominant aggressive malignancies of the gastrointestinal tract.^{90,91} CircRNAs have been studied to serve as biomarkers of diagnosis and treatment for ESCC and been involved in the regulation of the cell proliferation, migration, invasion and metastasis of ESCC.^{92,93} Increasing number of studies have shown that circRNA modulated the occurrence and progression of ESCC via acting as “miRNA sponge.” For example, circ-TTC17, deriving from tetratricopeptide repeat domain 17 (TTC17) gene, showed to promote proliferation and migration of ESCC cells by serving as “miRNA sponge.” The bioinformatics analysis observed a network of circ-TTC17 with its targeted miRNA interactions and corresponding mRNAs, and found that a total of 20 miRNAs were predicted to have binding sites with circ_TTC17 suggesting that circ-TTC17 might regulate progress of ESCC by acting as a sponge for miRNAs.⁹⁴ Moreover, circ-PRKCI promoted cell migration and proliferation through enhancing the expression of AKT serine/threonine kinase 3 by sponging miR-3680-3p in ESCC cells.⁹⁵ Circ_0006168 could regulate the mammalian target of rapamycin (mTOR) expression by sponging miR-100 to facilitate ESCC cell proliferation, migration and invasion. Thus, circ_0006168 has been considered to be a promising prognostic biomarker and effective therapeutic target for ESCC patients.⁹⁶ In line with this, other studies also found that circRNAs, such as circ-DLG1, circular RNA ciRS-7, circ_0000337, could interact with miRNAs by acting as sponge or competing endogenous RNA in the progression of ESCC.^{97–99} Together, these findings suggested that circRNA were involved in the carcinogenesis and progression of ESCC, and could be a promising diagnostic biomarker and potential therapeutic target in patients with ESCC.

Gastric Cancer

Gastric cancer (GC) is one of the most common malignant tumors in the digestive system and most GC is found at an advanced stage, which poses a great challenge to the treatment of this malignancy.^{100,101} An increasing number of studies have suggested that circRNA play critical roles and act as potential biomarker for the diagnosis and treatment of GC.^{102–104} However, the functions and underlying mechanisms of circRNAs in GC remain to be further studied. Likewise, “miRNA sponge” is also the main mechanism of circRNAs to participate in the progression of GC. For

instance, circYAP1 was identified to suppress cell proliferation and invasion of GC by sponging miR-367-5p, then inhibited the expression of p27^{Kip1}.¹⁰⁵ Also, circNRIP1 was found to sponge miR-149-5p to further regulate AKT/mTOR signaling axis and effected the cell proliferation, migration and invasion in GC.¹⁰⁶ Likewise, several other circRNAs such as circ_00610, circ-NOTCH1, circ-DCAF6, circ_0008035, circ_0001368, circPSMC3, circ-NF1, circ-SFMBT2, circFAT1(e2), circPDSS1, circ_0027599, and circ-0081143, could also serve as “miRNA sponge” to modulate other gene expressions in GC.^{107–118}

In addition, circRNA could also perform the biofunctions by serving as protein scaffolding in the progression pathogenesis of GC. For example, circ-DONSON was identified to promote cell proliferation, migration and invasion while inhibiting cell apoptosis in GC. Mechanistically, circ-DONSON could significantly recruit the NURF complex by acting as a protein scaffolding, to regulate a transcription factor Sex-determining region Y (SRY)-related high-mobility group box 4 (SOX4) promoter activity and stimulate transcription.¹¹⁹ Moreover, circAGO2, deriving from Argonaute 2 (AGO2), the core component of miRNA-induced silencing complex, physically interacted with human antigen R (HuR) protein to activate its activities and enrichment on the 3'-UTR of target gene, which significantly reduced the binding activation of AGO2 and thereby overcoming the effect of AGO2/miRNA-mediated gene silencing that was associated with the progression of GC.¹²⁰ Overall, circRNA played an important role in the tumorigenesis and progression through multiple mechanisms, and unveiled significant potential for the prevention and treatment of GC.

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is one of the most common cancers and the second cause of cancer mortality worldwide; nearly two-thirds of all patients with HCC are diagnosed at advanced stages.^{121–123} Growing evidences indicated that the expression alterations of circRNAs have a significant impact on biological characteristics of HCC. Recent study showed that circ-ZEB1.33 was a potential biomarker for the prognosis of HCC patients. They found that the expression of circ-ZEB1.33 was related to different TMN stages in HCC patients. Moreover, there were significant interactions between circ-ZEB1.33 and miR-200a-3p, as well as cyclin-dependent kinase 6 (CDK6) indicating that circ-ZEB1.33-miR-200a-3p-CDK6 regulatory pathway played a critical role in the progression of HCC.¹²⁴

Increasing number of studies have focused circRNA on their functions as efficient miRNA sponges in HCC as well. For example, circHIAT1 could act the miR-3171 sponge to further regulate the expression of PTEN that was a target of miR-3171, thereby inhibiting cell growth of HCC.¹²⁵ Likewise, circRNAs, such as circ_0101432 sponge miR-1258/miR-622,¹²⁶ circZNF652 sponge miR-203/miR-502-5p,¹²⁷ circSETD3 sponge miR-421,¹²⁸ circ_103809 sponge miR-620,¹²⁹ circ_0000267 sponge miR-646,¹³⁰ circ_0008450 sponge miR-548p,¹³¹ circDAMTS13 sponge miR-484,¹³² circ_0078710 sponge miR-31,¹³³ circ_101280 sponge miR-375,¹³⁴ circSLC3A2 sponge miR-490-3p,¹³⁵ and circTRIM33-12 sponge miR-191¹³⁶ have also been shown. All of these circRNAs were involved in the occurrence and progression of HCC by acting as “miRNA sponge.” In addition, some circRNAs could serve as immune-associated biomarker to regulate the tumorigenesis and metastasis. For example, circARSP91 regulated the progression of HCC through enhancing the activation of natural killer (NK) cells and increasing the susceptibility of HCC cells to NK cell cytotoxicity associated with cell immune surveillance.¹³⁷ Overall, circRNAs played key roles in tumorigenesis and development, epigenetic regulation, drug resistance, and could be considered as immune-associated biomarker and therapeutic target in HCC.^{138–144} Regardless, more in-depth study of circRNA biofunctions in HCC is greatly desired.

Bladder Cancer

Bladder cancer is the 9th most common cancer around the world with an estimated 165,000 deaths per year.^{145,146} Increased number of studies indicated that circRNAs were involved in the occurrence and development of bladder cancer.^{147–150} For instance, circUVRAG derived from the exon from the UV radiation resistance-associated gene (UVRAG) was highly increased in bladder cancer cells, and regulated the aggressive biological phenotype through targeting the miR-223/fibroblast growth factor receptor 2 (FGFR2) signaling pathway. Downregulation of circUVRAG promoted miR-223, but suppressed FGFR2 expressions.¹⁵¹ Circ-BPTF was also increased in bladder cancer tissues compared with noncancerous ones, and promoted the progression and recurrence of bladder cancer by regulating the miR-31-5p/RAB27A signaling pathway.¹⁵² Moreover, circLPAR1 inhibited the activity of miR-762 by directly binding to miR-762 thereby regulating invasion and metastasis of muscle-invasive bladder cancer cells.¹⁵³

circRNA-cTFRC regulated cell invasion and proliferation through acting as a ceRNA for miR-107 to affect the expression of TFRC expression in bladder cancer cells.¹⁵⁴ CircUBXN7 showed to inhibit the proliferation and invasion of bladder cancer cells through binding to miR-1247-3p to elevate the expression of β -1, 4-Galactosyltransferase III (B4GALT3), which is the direct target gene of miR-1247-3p.¹⁵⁵ Thus, circRNAs were involved in regulation of bladder cancer progression by serving as ceRNA. Interestingly, circRNAs could be also involved in the bladder oncogenesis and metastasis through regulating self-renewal function of cancer stem cells (CSCs). For example, knockdown of circGprc5a, a circRNA with peptide-coding potential and functions through a peptide-dependent manner, impaired the self-renewal and metastasis of bladder CSCs.¹⁵⁶ Together, data demonstrated that circRNA may provide a potential biomarker and therapeutic target for the management of bladder cancer.

Pancreatic Cancer

Pancreatic cancer is one of the most common malignancy and the fourth leading cause of cancer-related death worldwide with low 5-year overall survival rate of less than 7%.^{157,158} An increasing number of studies showed that circRNAs were associated with the occurrence and progression of pancreatic cancer.^{157,159} Circ-LDLRAD3 was reported to be increased in both cells and tumor tissues. High expression of circ-LDLRAD3 was significantly associated with venous invasion, lymphatic invasion and metastasis, indicating that circ-LDLRAD3 might be a critical biomarker in the diagnosis and treatment of pancreatic cancer.¹⁶⁰ Circ_0006215 was also regulated the progression of pancreatic cancer cells through the circ_0006215/miR-378a-3p/serpina family A member 4 (SERPINA4) signaling pathway.¹⁶¹ Moreover, circRNA_100782 regulated the miR-124/IL6/STAT3 pathway. Knockdown of circRNA_100782 significantly modulated miR-124 expression, and reduced miR-124 target genes interleukin-6 receptor (IL-6R) and STAT3 expressions in pancreatic cancer cells.¹⁶² Similarly, knockdown of circZMYM2 significantly repressed the tumorigenesis through sponging miR-335-5p, followed by affecting the expression of histone lysine demethylases jumonji domain-containing 2c (JMJD2C), which is the target gene of miR-335-3p in pancreatic cancer cells.¹⁶³ In line with this, the results of bioinformatics analysis showed that miR-26b-3p, miR-125a-3p, miR-330-5p and miR-

382-5p had binding sites for circRHOT1 suggesting that circRHOT1 might act as “miRNA sponge” to promote proliferation and invasion in pancreatic cancer cells.¹⁶⁴ In addition, exosomal circRNAs also contributed to tumor invasion and metastasis. For example, exosomal circ-PDE8A stimulated cell growth and invasive ability by acting as ceRNA to sponge miR-338 and regulated miR-338/metastasis-associated in colon cancer-1 (MACC1)/MET or hepatocyte growth factor (HGF) receptor regulatory axis in pancreatic cancer cells.¹⁶⁵ Moreover, exosomal circ-IRAS significantly promoted invasion and metastasis of pancreatic cancer cells by down-regulating miR-122 and ZO-1 levels, and up-regulating RhoA and RhoA-GTP levels, F-actin expression, regulating endothelial monolayer permeability.¹⁶⁶ We believed that circRNAs could provide a new promising biomarker for diagnosis and therapeutic target for the treatment of pancreatic cancer.

Papillary Thyroid Carcinoma

Thyroid cancer is one of the most common malignant endocrine tumors, with an incidence of 1–2% of all types of cancer. Despite of a good and overall prognosis, papillary thyroid cancer (PTC), which accounts for 75% of thyroid cancer, could still affect the quality of life of PTC patients.^{167,168} A large number of circRNAs showed promising as potential prognostic biomarkers for the PTC patients, and played a critical role in the pathogenesis and progression of PTC.^{169–171} For example, knockdown of circBACH2 inhibited the cell proliferation, migration and invasion of PTC cells in vitro and suppressed the growth of PTC xenografts in vivo. Mechanistically, circBACH2 directly interacted with miR-139-5p and relieved inhibition of its target gene LIM-domain only protein 4 (LMO4). Therefore, circBACH2/miR-139-5p/LMO4 regulatory axis could be a promising treatment strategy for PTC patients.¹⁷² Likewise, low expression of circRAPGEF5 plays an important role in suppressing the aggressive biological behaviors of PTC by sponging miR-198, this subsequently downregulated the expression of fibroblast growth factor receptor 1 (FGFR1), a target gene of miR-198.¹⁷³ Moreover, overexpression of circ_0025033 promoted proliferation and invasion of PTC by directly sponging miR-1231 and miR-1304, therefore, circ_0025033/miR-1231/miR-1304 signaling pathway was considered to be a new regulatory mechanism in PTC initiation and progression.¹⁷⁴ Recent study found that knockdown of circRNA_102171 inhibited PTC

progression. CircRNA_102171 could interact with catenin beta interacting protein 1 (CTNNBIP1) and block its association with the β -catenin/TCF complex to further activate the activity of Wnt/ β -catenin pathway in PTC cells.¹⁷⁵ In a similar way, circ-ITCH was also correlative with Wnt/ β -catenin pathway. Bioinformatics analysis and luciferase reporter assays showed that circ-ITCH could sponge miR-22-3p to increase the expression of CBL, an E3 ligase of nuclear β -catenin. This led to suppress activation of the Wnt/ β -catenin pathway and consequently inhibited the progression of PTC.¹⁷⁶ Moreover, circZFR was negative correlated with clinical severity of PTC patients. Knockdown of circZFR significantly activated C8orf4 (chromosome 8 open reading frame 4), an activator of Wnt signaling pathway via sponging miR-1261 thereby inhibiting proliferation, migration and invasion of PTC cells.¹⁷⁷ In addition, circ_0058124 acted as a ceRNA to directly regulate the expression of miRNA-218-5p and its target gene NUMB, and consequently inhibited the activation of the NOTCH3/GATA zinc finger domain-containing 2A (GATAD2A) signaling axis. This led to promote cell proliferation, tumorigenicity, invasion, and metastasis of PTC, thus highlighting a novel therapeutic target for intervening PTC.¹⁷⁸ Growing evidences have also shown that circRNA not only play an important role in carcinogenesis and development of PTC, but also have great diagnostic and prognostic value for PTC. One study showed the expression of circRNAs in PTC tissues and adjacent non-cancerous tissues, and assess the diagnostic value of circRNAs through analyzing the correlation between circRNAs and aggressive clinic-pathologic characteristics of PTC indicated that circ_0137287 had a potential diagnostic value in predicting severity of malignancy, extra thyroidal extension and lymph node metastasis, and may act as a novel biomarker for PTC.¹⁷⁹ Taken together, circRNA might play an important role in the progression and pathogenesis and be considered as potential biomarkers of PTC.

Osteosarcoma

Osteosarcoma is a malignant bone tumor that has the highest morbidity in adolescent and childhood with 60% of patient aged under 25 years; however, there is a second peak of incidence in later life with 30% of patients being over 40 years of age.^{180–182} Several studies have indicated the correlations between circRNA and occurrence and progression of osteosarcoma.^{183–185} CircFAT1, deriving from exon 2 of FAT atypical cadherin 1 (FAT1) gene,

significantly inhibited the cell migration, invasion and tumorigenesis of osteosarcoma by sponging miR-375 to enhance the expression of yes-associated protein 1 (YAP1) protein.¹⁸⁶ Similarly, knockdown of circCDR1as significantly suppressed tumor growth of osteosarcoma through directly targeting miR-7 and subsequently reduced EGFR, Cyclin E1 (CCNE1), phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit delta (PI3KCD) and RAF1 proto-oncogene serine/threonine-protein kinase (RAF1) expressions.¹⁸⁷ As we know, transcription factor CREB3 is a driver gene in osteosarcoma. CircTADA2A could upregulate the expression of CREB3 by sponging miR-203-3p thereby significantly promoting the progression and metastasis in osteosarcoma cells.¹⁸⁸ In addition, circ_0081001 was highly expressed in the osteosarcoma tissues and cells, which may be a potential biomarker for diagnosis and therapeutic target of osteosarcoma. Moreover, serum circ_0081001 might be a better diagnostic and independent prognostic factor than alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) in osteosarcoma patients.¹⁸⁹ More importantly, some of circRNAs are closely related to chem-resistance of osteosarcoma. For example, upregulation of circ_001569 not only promoted cell proliferation, but also enhanced the cisplatin resistance of osteosarcoma cells through activating the Wnt/ β -catenin signaling pathway.¹⁹⁰ Thus, the abnormal expression of circRNAs is an important factor in regulating the occurrence and development of osteosarcoma. We believed that circRNA could be served as the valuable biomarker for the prevention, diagnosis and treatment of osteosarcoma in the future.

Glioblastoma

Glioblastoma is the most common and fatal primary malignant brain tumor. The published data have shown a strong association between circRNA and glioblastoma. The results from microarray analysis showed that most circRNAs were dysregulated in glioblastoma. circ_0001946 was downregulated in glioblastoma and overexpression of circ_0001946 significantly inhibited cell proliferation, migration, invasion and induced apoptosis through upregulating the expression of cerebellar degeneration-related auto-antigen 1(CDR1) by suppressing miR-671-5p expression in glioblastoma cell.¹⁹¹ Obviously, circRNA could also act as “miRNA sponge” to regulate glioblastoma progression. CircMMP9 could regulate the expression of eukaryotic initiation factor 4A3 (eIF4A3) to further accelerate proliferation,

migration and invasion via sponging miR-124 in glioblastoma cells.¹⁹² Moreover, circNT5E, deriving from ecto-5'-nucleotidase (NT5E) gene and regulating by adenosine deaminase, RNA-specific B2 (ADARB2), also acted as the sponge of miR-422a and reduced its expression, thereby promoting glioblastoma tumorigenesis.¹⁹³ Furthermore, circ_0029426 served as the sponge of miR-197 to promote cell proliferation, migration and invasion, inhibited cell apoptosis of glioblastoma cells as well.¹⁹⁴ Taken together, acting as “miRNA sponge” is one of the most important functions and mechanisms for circRNA to modulation of miRNA and downstream target gene. Recently, comparative results of circRNAs expression profiles showed that 254 circRNAs were up-regulated and 361 circRNAs were down-regulated in IDH-wt glioblastoma compared with the adjacent normal brain tissues. Gene Ontology (GO) analysis revealed that differential expressions of circRNAs were correlated with cell division, DNA damage repair, cytoskeleton, and protein ubiquitination.¹⁹⁵ Their results suggested that differential expressions of circRNAs might serve as biomarkers for prognosis and treatment targets for IDH-wt glioblastoma.¹⁹⁵ In addition, there was evidence that endogenous circRNA was involved in gene translation. CircRNA containing an ORF could translate a functional protein through driving by Internal Ribosome Entry Site (IRES) elements.¹⁹⁶ For example, circ-SHPRH could produce a 17 kDa protein, the circular form of the SNF2 histone linker PHD RING helicase (SHPRH) gene encoded a novel protein that we termed SHPRH-146aa, which was a tumor suppressor in human glioblastoma. Excessive expressed SHPRH-146aa reduced malignant behavior and tumorigenicity in U251 and U373 glioblastoma cells by protecting SHPRH from degradation through the ubiquitin proteasome. An increased patient survival was observed with elevated levels of SHPRH-146aa in glioblastoma patients.^{196,197} Collectively, these results showed that circRNA was a group of important regulatory factor and related to the occurrence and progression of glioblastoma. Thus, circRNA could serve as potential and valuable biomarker for diagnosis and treatment for glioblastoma patients in the future.

Ovarian Cancer

Ovarian cancer is the leading cause of death from gynecological malignancies worldwide. The overall 5-year survival rate was particularly low for patients with advanced stages. In recent years, numerous studies focused on

differentially expressed circRNAs and their function in this malignancy indicating that circRNAs may act as potentially novel biomarkers or therapeutic agents in this cancer type.¹⁹⁸ Increasing number of circRNAs have been reported to be involved in the progression and tumorigenesis of ovarian cancer. One study revealed that circPUM1 promoted cell proliferation, migration, invasion, and metastasis through increased the expression of nuclear factor kappa B (NF- κ B) and matrix metalloproteinase 2 (MMP2) by sponging miR-615-5p and miR-6753-5p in ovarian cancer cells.¹⁹⁹ CircWHSC1 increased proliferation, migration and invasion, and inhibited apoptosis by sponging miR-145 and miR-1182 thereby increasing the expression of downstream targets mucin 1 (MUC1) and human telomerase reverse transcriptase (hTERT) in ovarian cancer cells.²⁰⁰ Similarly, scores of circRNAs performed their biological functions through acting as sponge of miRNAs in ovarian cancer, such as circUBAP2 sponge miR-144, circCDR1 sponge miR-135b-5p, circ-CSPP1 sponge miR-1236-3p, circ_0051240 sponge miR-637, circEPSTI1 sponge miR-942, circ-ITCH sponge miR-10a, circ_0061140 sponge miR-370, and circGFRA1 sponge miR-449a.^{201–208} In addition, study showed that circSETDB1 expression levels were closely associated with advanced clinical stage and lymph node metastasis of high-grade serous ovarian cancer patients. Patients with higher levels of circSETDB1 had a shorter progression-free survival time. Thus, circSETDB1 might be a promising biomarker for the treatment and relapse in high-grade serous ovarian cancer.²⁰⁹ Moreover, upregulation of circ-FAM53B accelerated the proliferation, migration, and invasion of ovarian cancer via regulating the miR-646/vesicle associated membrane protein 2 (VAMP2) and miR-647/mouse double minute 2 (MDM2) signaling regulatory pathways.²¹⁰ Also, circPLEKHM3 could inhibit cell growth, migration and EMT via miR-9/BRCA1/DnaJ/Hsp40 homolog, subfamily B, member 6 (DNAJB6)/Kruppel-like factor 4 (KLF4)/AKT1 regulatory axis in ovarian cancer suggesting that circPLEKHM3 might act as a prognostic indicator and therapeutic target in ovarian cancer patients.²¹¹ In addition, circ-SMAD7 enhanced cell metastasis, proliferation and progression of ovarian cancer via suppressing the expression of Kruppel-like factor 6.²¹² Overall, the differentially expressed circRNAs may participate in the pathogenesis of ovarian cancer, and may be novel diagnostic and prognostic biomarkers for ovarian cancer although more studies are still needed to be evaluated.

Prostate Cancer

Prostate cancer (PCa) is one of the most common cancers and the third leading cause of deaths with high mortality and morbidity, especially for elderly men around the world.^{213,214} CircRNAs play important roles in the regulation of cell proliferation, apoptosis, angiogenesis and metastasis in a series of cancers including prostate cancer. Most of them could be used for the promising biomarkers and therapeutic target for the treatment of prostate cancer.²¹⁵ One recent study have found that circITCH was significantly down-regulated in PCa cells and tissues, and inhibited the malignant phenotype of PCa via increasing the expression of homeobox protein B13 (HOXB13) through sponging miR-17-5p.²¹⁶ Likewise, circRNA-UCK2 inhibited cell proliferation and invasion via increasing tet methylcytosine dioxygenase 1 (TET1) expression by sponging miR-767-5p in prostate cancer.²¹⁷ Similarly, circFOXO3 sponged miR-29a-3p, circABCC4 sponged miR-1182, circHIPK3 sponged miRNA-338-3p and miR-193a-3p, and circAMOTL1L sponge dmiR-193a-5p were also reported in other studies.^{218–222} This may be one the main mechanisms of circRNAs to function as miRNA sponges in many cancers including prostate cancer. Moreover, circ_KATNAL1 significantly inhibited cell proliferation, invasion, migration of prostate cancer through the miR-145-3p/Wnt1 inducible signaling pathway protein 1 (WISP1) pathway, which might be a new mechanism for the progression of prostate cancer.²²³ More interestingly, recent study revealed that some of circRNAs could perform their functions by cooperating with their host genes. For example, X-linked inhibitor of apoptosis protein (XIAP), a host gene for circRNA0005276, showed to interact with circ0005276 to mediate the progression of prostate cancer through activating the transcription of XIAP via interacting with FUS binding protein.²²⁴ Thus, circRNAs are important regulators in gene expression and play a crucial role in prostate cancer, however, the detailed mechanisms for the tumorigenesis and progression should be more explored in the future.

Myeloid Leukemia

There are two main types of myeloid leukemia, acute myeloid leukemia (AML) and chronic myeloid leukemia (CML). AML is one of the most common myeloid malignancy in adults, characterized by the proliferation of abnormal and immature myeloid blasts in the bone

marrow and presented great biological and clinical heterogeneity.²²⁵ CircRNAs were served as potential biomarkers for the diagnosis and treatment of AML because of their stability against exo-nuclear degradation, diversity of action modes, tissue specificity and richness in body fluids.^{225,226} Through high-throughput sequencing and bioinformatics analysis, 1824 circRNAs were detected as differentially expressed in AML cells.²²⁷ In addition, a total of 273 circRNAs were increased and 296 were decreased in pediatric AML. Among them, circ-0004136 was significantly increased and promoted cell proliferation by acting as a sponge of miR-142.²²⁸ Similarly, the following circRNAs also function as a miRNA sponge in acute myeloid leukemia, such as circ_0009910 sponging miR-20a-5p, circ_100290 sponging to miR-203 and circ-ANAPC7 sponging to miR-181.^{229–231} Furthermore, recent studies observed that circ-Foxo3 could compete with Foxo3 for binding to some miRNAs and then regulated the expression of Foxo3.²³² Circ-Foxo3 and Foxo3 were frequently decreased in AML and positively associated with each other. Circ-Foxo3 might be a promising biomarker for the prognosis and treatment of AML.²³³ In addition, some circRNAs might be related to drug resistance in acute myeloid leukemia. For example, silence of circPAN3 significantly restored drug sensitivity to ADM in the two ADM-resistant cell lines, and over-expression of circPAN3 had the opposite effect. The results suggested that circPAN3 might facilitate AML drug resistance through regulating the AMPK/mTOR signaling pathway.²³⁴ In chronic myeloid leukemia (CML), recent study found that expressions of circHIPK3 and circRNA_100053 were significantly increased compared with healthy controls. Induced circHIPK3 expression predicted a poor outcome of CML patients, and circ_100053 might be associated with imatinib resistance in CML.^{235,236} In addition, circ_0080145 was found to be up-regulated in CML, and silence of circ_0080145 significantly inhibited cell proliferation of CML by sponging miR-29b.²³⁷ Taken together, circRNAs were distributed broadly in myeloid leukemia, and abnormal expressions of circRNAs were closely related to the progression and tumorigenesis of myeloid leukemia including AML and CML. Nevertheless, further studies are still required to determine the potential roles of circRNAs in diagnostic biomarker and therapeutic targets.

circRNAs in Cancer Stem Cells

Cancer stem cells (CSCs), a small proportion of cells that possess self-renewal and tumor-initiating capabilities, are considered to be responsible for metastatic dissemination and therapeutic failure. Several lines of evidence have suggested that circRNAs might contribute to the stemness of cancer.²³⁸ For example, around 27 dysregulated circRNA were observed through high-throughput sequencing to screen the circRNA expression profiles in breast CSCs (BCSCs) and matched non-BCSCs. Among these, expression of circVRK1 was reduced and was able to inhibit the self-renewal capacity of BCSCs, thereby displaying an inhibiting role in the stemness of BCSCs. Breast cancer cells with silenced circVRK1 demonstrated an enhanced capacity to form mammospheres and colonies, and an increased expression of CSC-related markers and core pluripotency genes (OCT4, SOX2, NANOG), indicating that circVRK1 was involved in suppressing the stemness of BCSCs.²³⁹ MiR-153-5p was one of the targets of circVRK1 and was involved in stemness maintenance of breast cancer cells via reducing the expression of KLF5. Thus, circVRK1 was negatively correlated with stemness of BCSCs through the miR-153-5p/krüppel-like factor 5 (KLF5) regulatory pathways.²⁴⁰ Stem cell plasticity and identity are also controlled by master regulatory genes and complex circuits involving circRNAs as well. One study showed that compared to differentiated mesodermal derivatives, circFOXP1 levels were enriched in mesenchymal stem cell (MSC) and silencing of circFOXP1 dramatically impaired MSC differentiation in vitro and in vivo. A direct interaction between circFOXP1 and miR-17-3p/miR-127-5p resulted in the modulation of the epidermal growth factor receptor (EGFR) and noncanonical Wnt pathways suggesting the regulatory role for circFOXP1 as a gatekeeper of pivotal stem cell molecular networks.²⁴¹ In addition, the underlying correlation between circRNAs and cancer stem cells (CSCs) has been reported in HCC. For example, the absence of circZKSCAN1 endowed several malignant properties including cancer stemness and closely correlated with poor overall and recurrence-free survival in HCC. Bioinformatics analysis and RNA immunoprecipitation-sequencing (RIP-seq) experiments revealed that circZKSCAN1 showed inhibitory role by competitively binding RBP fragile X mental retardation protein (FMRP), thereby blocking the binding between FMRP and the downstream target gene cell cycle and apoptosis

regulator 1 (CCAR1) mRNA, and subsequently retarded the transcriptional activity of Wnt signaling resulting in suppressing cell stemness in HCC cells.²⁴² CD133+CD44 + cancer stem cells (TDP cells) previously isolated from laryngeal squamous cell carcinoma (LSCC) cells showed strong malignancy and tumorigenicity. These TDP cells were shown to highly express the stem-cell markers SOX2 and OCT4. Hg19_circ_0005033 was one of the upregulated circRNAs in TDP cells promoted the proliferation, migration, invasion, and resistance to chemotherapy of TDP cells.²⁴³ The expression of stem cell marker Kruppel-like factor-4 (KLF-4), which has been reported as the target of miR7, increased significantly in ciRS-7 transfected ESCC cells. Knockdown of KLF-4 also attenuated over expression of ciRS-7 induced cell invasion.⁹⁸ Overall, the potential regulatory mechanism of circRNAs in CSC phenotypes and potential clinical applications in CSC-targeted therapy, including functioning as new biomarkers, acting as vaccines and breaking the therapeutic resistance of CSCs have been summarized.²⁴⁴ Researches regarding the regulatory roles of circRNAs on CSCs are still in the initial stages although the increased numbers of studies have demonstrated that the aberrant expression of circRNAs play a key role in the regulation and progression of cancers and CSCs. Thus, the practical application of circRNAs in clinic arena still remains to be determined. Future studies are needed to explore how circRNAs change in the CSC environment, among others.

Discussion and Prospective

CircRNAs have attracted increasing attention over the last decade. With the rapid development of biotechnology, bioinformatics analysis and publicly available high-throughput RNA-Seq data from the ENCODE consortium, a large numbers of circRNAs have been identified in recent years. CircRNAs can be detectable in body fluids, such as blood and saliva, urine, and breast milk including membrane-bound vesicles, such as exosome, and has widely involved in a variety of cancer-related physiological and pathology processes, including cancer initiation, progression and metastasis, drug resistance and played an important role in the diagnostic and prognostic biomarker and the therapeutic target in human cancer.^{245–247} It has become increasingly clear that circRNAs regulate gene expression through various actions and play diverse roles in many fields of human cancer biology. Recently, investigating the presence and expression levels of exosomal circRNAs could allow us to discriminate cancer patients

from healthy individuals, identifying new potential exosome-based cancer biomarkers.²⁴⁸ Exosomal circRNAs are a novel frontier in cancer research and exploring the mysterious connection of exosome and circRNA may provide a vital hint to understand the biological functions of exosomal circRNAs. New studies show that exosomal circRNAs originating from tumor cells or other cells can transfer biological information to the specific cells to achieve the efficient transmission of phenotypical changes and thereby promoting cancer metastasis. Taking advantage of the stability and high specificity of exosomal circRNAs, these molecules might serve as promising cancer biomarkers with early detection and powerful prediction for patients to receive the most suitable therapy and might have potential for monitoring cancer progression or recurrence, and even to successfully develop therapeutic methods for the treatment of cancer although gaps in our current understanding of the connection of circRNAs with exosome still remain, such as the mechanism by which exosomal circRNAs travel in bodily fluids and the roles of exosomal circRNAs in cancer. Upon complete elucidation of exosomal circRNA functionality and molecular mechanisms relevant to human cancer, avenues of new insight will be opened, providing novel therapeutic approaches in malignant tumors.¹¹

CircRNAs may also play a key role in the development of drug resistance. Recently, multiple studies have highlighted the key roles of ncRNAs in chemoresistance of cancer, such as HCC,^{142,249} lung cancer,^{250,251} gastric cancer,^{252,253} breast cancer,^{254,255} multiple myeloma,²⁵⁶ acute myeloid leukemia,²³⁴ prostate cancer,²⁵⁷ bladder cancer,²⁵⁸ among others. The up-to-date information regarding the role of circRNAs in the resistance of tumors to chemotherapy has been recently summarized with multiple mechanisms, such as modulating various regulatory pathways and processes including the ceRNA regulatory network axis, EMT process, regulation of ABC transporters, apoptosis, autophagy, and CSCs, among others although many physiological processes and biological signaling pathways through which circRNAs are involved in drug resistance still remained unknown.²⁵⁹ Thus, more mechanisms of action of chemoresistance-related circRNAs need to be explored in the future.

Importantly, the unique cellular stability and function of circRNAs to sponge miRNA and proteins may also indicate that circRNA is a promising vehicle for targeted drug delivery.⁴ So far, there has been no preclinical data demonstrating that circRNAs alone have been used as

targets or therapeutic vectors for cancer treatment, but this direction will likely show promising in the future. The unique cellular stability and capacity of circRNA to sponge miRNA and protein may place circRNA as a promising vehicle for the delivery of cancer therapeutics. It is reasonable to believe that circRNAs will bring a new revolution for the diagnosis and treatment of human cancer in the near future.

However, there are also a number of challenges that need to be addressed. First of all, the expression level of most circRNAs are relative low in human cancer, therefore, we will require more advanced and sensitive technologies and tools to detect the molecular function of specific circRNA in the future.¹⁰ Secondly, owing to the fact that the majority of circRNA sequence is shared with the mRNA generated from the host gene. Hence, there are some troublesome technical problems need to be solved, such as circRNA quantification and validation, as well as overexpression and silencing strategies.^{10,260} Thirdly, the names of many circRNAs have not yet been standardized. As a result, many independent studies cannot be unified and generalized, which were not conducive to the sustainability and refer ability of circRNA research.²⁵ Finally, the study of circRNAs in cancer is still in its infancy, and the functional role and mechanism of circRNA in distinct human cancers remains unclear. The current knowledge of circRNAs in tumorigenesis as well as their potential in diagnostic and prognostic biomarkers and possible therapeutic targets still remained to be elucidated. Thus, the in-depth underlying mechanism of circRNA in cancer biology needs to be explored further. It also speculated that the aberrant expression of circRNAs observed in cancer might also be explained by genetic and/or epigenetic changes of genes involved in their biogenesis. By addressing these issues and challenges with the advanced technology, improved experimental approaches and further research, we believe that circRNA could become a medically valuable diagnostic tool and an effective biological target for various cancers in the near future. Therefore, revealing cancer pathogenesis mechanisms and seeking novel potential diagnostic biomarkers or therapeutic targets will be popular topics in the future.²⁶¹ Future detection of circRNA should also be explored the utilities of some new technologies, such as Oxford Nanopore sequencing, which can potentially provide information on the entire circRNA and could be an important addition to the mammalian transcriptomics toolbox²⁶² and the NanoString nCounter Analysis

System, which can quantify RNA molecules quantitative data output without amplification and reverse transcription.^{4,263} In conclusion, this study describes major features of circRNAs, summarizes the biological functions and mechanisms of circRNA associated with the occurrence, growth, progression, metastasis, drug resistance of human cancers. CircRNA can be used as potential diagnostic, prognostic biomarker and therapeutic target for personalized therapeutic for human cancer.

Abbreviations

circRNA, Circular RNA; MDM2, mouse double minute 2; RBPs, RNA-binding proteins; 3'UTRs, 3'-untranslated regions; ILF2/3, interleukin enhancer-binding factor 2 and 3 complex; ITGA7, integrin alpha 7; RREB1, RAS-responsive element-binding protein 1; NSCLC, non-small cell lung cancer; NOVA1, NOVA alternative splicing regulator 1; snRNA, U1 small nuclear RNA; ORF, open reading frame; IRES, internal ribosome entry site; STAT3, signal transducer and activator of transcription 3; PRKAA, protein kinase AMP-activated catalytic subunit alpha 2; AMPK α , AMP-activated protein kinase; RBPs, RNA-binding proteins; RBM3, RNA-binding protein 3; SCD, stearoyl-CoA desaturase; RPCs, RNA-protein complexes; CDK2, cyclin-dependent kinase 2; SCML1, sex comb on midleg-like 1; HN, humanin; EMT, epithelial mesenchymal transitioning; RASSF8, ras association domain family 8; EML4-ALK, echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase; ceRNA, endogenous RNA; BC, breast cancer; TRAF, TNF α receptor associated factor; TNBC, triple-negative breast cancer; CRC, colorectal cancer; RNA-seq, RNA sequencing; APC2, adenomatous polyposis coli 2; CRR, chemoradiation resistance; ESCC, Esophageal squamous cell carcinoma; TTC17, tetratricopeptide repeat domain 17; mTOR, mammalian target of rapamycin; GC, gastric cancer; SRY sex-determining region Y; SOX4, SRY-related high-mobility group box 4; AGO2, argonaute 2; HuR, human antigen R; HCC, hepatocellular carcinoma; CDK6, cyclin-dependent kinase 6; NK, natural killer; UVRAG, UV radiation resistance associated gene; FGFR2, fibroblast growth factor receptor 2; B4GALT3, β -1, 4-Galactosyltransferase III; CSCs, cancer stem cells; SERPINA4, serpina family A member 4; IL-6R, interleukin-6 receptor; JMJD2C, jumonji domain containing 2c; MACC1, metastasis-associated in colon cancer-1; HGF, hepatocyte growth factor; PTC, papillary thyroid cancer; LMO4, LIM-domain only protein 4; FGFR1, fibroblast

growth factor receptor 1; CTNBP1, catenin beta interacting protein 1; C8orf4, chromosome 8 open reading frame 4; GATAD2A, GATA zinc finger domain containing 2A; FAT1, FAT atypical cadherin 1; YAP1, yes-associated protein 1; CCNE1, Cyclin E1; PI3KCD, phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit delta; RAF1, RAF1 proto-oncogene serine/threonine-protein kinase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; CDR1, cerebellar degeneration-related auto-antigen 1; ADAR2, adenosine deaminase, RNA-specific B2; GO, Gene Ontology; SHPRH, SNF2 histone linker PHD RING helicase; SOCS3, suppressor of cytokine signaling 3; RIP-seq, RNA immunoprecipitation-sequencing; CCAR1, cell cycle and apoptosis regulator 1; FMRP, fragile X mental retardation protein; EGFR, epidermal growth factor receptor; MSC, mesenchymal stem cell; KLF5, krüppel-like factor 5; BCSCs, breast CSCs; KLF-4, Kruppel-like factor-4; ecRNAs, exonic circRNAs; ciRNAs, intronic circRNAs; elciRNAs, exon-intron circRNAs; LSCC, laryngeal squamous cell carcinoma; TDP cells, CD133+CD44+ cancer stem cells; NF- κ B, nuclear factor kappa B; MMP2, matrix metalloproteinase 2; MUC1, mucin 1; hTERT, human telomerase reverse transcriptase; VAMP2, vesicle-associated membrane protein 2; MDM2, miR-647 mouse double minute 2; DNAJB6, DnaJ/Hsp40 homolog, subfamily B, member 6; PCa, prostate cancer; HOXB13, homeobox protein B13; TET1, tet methylcytosine dioxygenase 1; WISP1, Wnt1 inducible signaling pathway protein 1; XIAP, X-linked inhibitor of apoptosis protein.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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